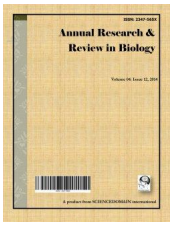

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Effect of Consumption of Artesunate and/or Palm Wine on Serum Electrolytes, Urea, Creatinine and Estimated Glomerular Filtration Rate

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Authors' contributions

This work was carried out in collaboration between all authors. Author EEO designed the study. Author DDA wrote first draft of the manuscript. Authors UEO and ABA wrote the protocol. Author DDA performed statistical analysis. Authors DDA and UEO managed the analyses of the study. Author UEO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Artesunate (artemisinin derivative) prophylaxis is one of the preferred treatments for malaria including *Plasmodium falciparum* malaria in Nigeria as well as other tropical and subtropical countries. Also widely consumed in the tropics for its taste and alcohol content is palm wine. It is not uncommon to find some individuals on artesunate medication consuming palm wine with the belief that such a combination makes malaria treatment more effective. Therefore, this study is aimed at assessing the effects of artesunate intake and palm wine consumption on renal function.
Study Design: Thirty participants aged 18 to 35 years were randomly assigned into 3 groups of 10 persons per group namely; palm wine and artesunate, palm wine only and artesunate only groups. Each group received their treatments for 7 days.
Methodology: This study employs the use of pre-treatment and post-treatment design, with each subject serving as its control. Serum levels of electrolytes, urea, creatinine and estimated glomerular

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filtration rate (eGFR) were assessed before and after 7 days of treatment. Participants were all Africans (n=30) and were the staff of the Faculty of Basic Medical Sciences, University of Calabar.
Results: Significant increase ($p<0.05$) in serum Na^+ and a decrease in K^+ levels above pretreatment values were observed in the palm wine and artesunate group. Creatinine concentrations of both palm wine and artesunate, as well as artesunate only groups, were significantly increased above control values. Creatinine clearance rate was significantly reduced ($p<0.05$) in the palm wine and artesunate group.
Conclusion: Combined consumption of fresh palm wine and artesunate decreased creatinine clearance rate as well as eGFR. This decrease may be followed by a decline in the other renal function indices.

Keywords: Palm wine; artesunate; creatinine; eGFR; serum electrolytes; kidney failure.

1. INTRODUCTION

Artesunate is a part of the three classes of antimalarials known as Artemisins (Artemisinin derivatives). This new generation antimalarial is a chemosynthetic derivative with improved potency and bioavailability.[1] Artemisinin is a sesquiterpene lactone endoperoxide derived from the weed qang hao (*Artemisia annua*) also called sweet wormwood or annual wood [1].

The drug reaches its peak serum levels within hours after administration and rapidly acts by significantly reducing malaria parasite burden in the first few days of treatment. The side effects of artemisinin medication are similar to the symptoms of malaria; nausea, vomiting, anorexia, body pains, dizziness and liver inflammation [2]. As a class of Artemisinins, artesunates are potent and fast acting antimalarials well suited for treatment of severe cases of *Plasmodium falciparum* malaria [3]. They also play vital role in combination with other antimalarials for first line treatment of malaria (including drug resistant ones) [4].

Palm wine is the sweet tasty sap obtained from different palm trees such as coconut palms, date palms, Palmyra and even the African oil palm (*Elaeis guineensis*). It is a widely consumed alcoholic beverage in various parts of Africa, Asia, the Caribbean and South America. It is known by various names in different regions where it is obtained. In Nigeria it is called *Ukọt nsuñ, Mmin efik, Nkwu enu, Nkwu ocha*. Palm wine is used in many ceremonies in parts of Nigeria, as well as other central and western African countries.

When fresh it tastes sweet, but begins fermenting immediately after collection owing to natural yeasts in the air. Within two hours of fermentation, it yields an aromatic wine of 4% alcohol content. Prolonged fermentation yields vinegar [5]. Alcohol does appear to directly influence the kidney's handling of sodium as well as other electrolytes and fluid [6,7].

The attitude of people in the treatment of malaria varies from region to region. Some locals in the bid to treat malaria and other forms of ailment ingest cocktails of palm wine with orthodox or herbal medication (personal observation). It is not uncommon to find some individuals on artesunate treatment or prophylaxis for malaria, consuming palm wine regularly with the belief that palm wine will bolster the effects of the drug. The nephrotoxicity of such combination has not been investigated.

The incidence of renal toxicity associated with the ingestion of unspecified drug combinations that lead to renal failure has been reported [8]. The present study was therefore aimed at evaluating not only the singular effects of palm wine and artesunate on serum electrolytes, urea, creatinine and estimated glomerular filtration rate but also the combined effects of palm wine and artesunate.

2. MATERIALS AND METHODS

2.1 Phytochemical Screening of Palm Wine

The phytochemical analysis of palm wine was carried out using standard procedures to determine the presence and levels of flavonoids, saponins, tannins, sugars and alcohol. The following tests were used for the phytochemical analysis; gravimetric (for saponins), spectrophotometric (for alcohol), Benedict (for reducing sugars), colour change (for flavonoids and tannins) tests [9,10,11].

2.2 Collection/Treatment

Artesunate tablets marketed under the trade name ARTESUNAT™ (Mangalam Drugs & Organics Ltd, Mumbai) were obtained from Bez Pharmacy, Calabar. Fresh palm wine was collected from a palm wine tapper in the locality where this study was conducted. Sixty ml of fresh palm wine (one hour after obtaining the sap) and 500 mg of artesunate tablets were administered once daily for 7 days to the participants in the different groups. The doses of palm wine and artesunate were similar to doses taken in the treatment of malaria. Prior to the administration of palm wine and artesunate tablets, blood samples were obtained from the subjects and serum electrolytes, urea, creatinine and estimated glomerular filtration rate were determined. After administration of palm wine and artesunate for seven days, serum electrolytes, urea, creatinine and estimated glomerular filtration rate were determined. Each subject served as its own control.

2.3 Study Design

The present study used a pre-treatment and post-treatment design to assess the effects of consumption of artesunate and/or fresh palm wine on serum electrolytes, urea, and creatinine and estimated glomerular filtration rate (eGFR) of 30 participants. Pre-treatment values obtained served as control values. The 30 participants (17 men and 13 women) aged between 18 to 35 years and selected randomly were chosen to preclude the composite effect of age related deterioration in renal function. These subjects were assigned to three groups of ten persons per group. The first group was administered palm wine and artesunate, while the second group received palm wine only, the third group was given artesunate only.

Informed written consent was obtained from each participant. This study was targeted at apparently healthy subjects with no visible signs of renal impairment. Each participant was made to undergo thorough pre-survey medical screening to ensure medical fitness and to exclude those who did not meet the inclusion criteria for this study, including those with malaria. Screening included determination of medical history, lifestyle assessment (drinking, smoking, physical activity and drug history). The subjects were advised to avoid excessive physical activity, ingestion of drugs or alcohol and to remain on their regular diet throughout this study.

The exclusion criteria used were: inappropriate age (<18 or >35 years), history of hypersensitivity or allergy to artesunate and palm wine, a history of kidney disease, pregnancy or lactation, use of drugs known to affect or can be metabolised in the kidney, chronic diseases (diabetes, hypertension and sickle cell anaemia).

2.4 Biochemical Estimation

Venous blood samples were obtained for biochemical analysis after 8 hours of fasting. Parameters measured were serum creatinine, urea and electrolytes. Serum creatinine level was assessed by Jaffe's method using 0.75 NaOH and 1% Picric acid at 1 mL each to the serum-specific specimen. A standard was similarly treated. Change in colour observed within 15 minutes was measured with a spectrophotometer (AC-ZE 18, Surgifriend Medicals Ltd., England) at 520nm. Serum urea was measured using multichannel automated analyzer. Renal function (eGFR) was assessed by using Serum creatinine estimation, estimation of glomerular filtration and calculation of creatinine clearance with the use of the Cockcroft-Gault formula [12] and adapted by Botev et al. [13].

2.5 Statistical Analysis

Data were analyzed by one-way analysis of variance and least significant difference test (LSD) using the Statistical Package for the Social Sciences (SPSS 20.0). Values were considered statistically significant at $P<.05$. All results derived were presented as mean $\pm$ SEM.

3. RESULTS

The demographic characteristics of the subjects showed that 30 subjects (17 men and 13 women) participated in the study. Other details are showed in Table 1.

Table 1. Pretreatment demographic characteristics of study participants

Characteristics	Values
Average age	26.5 $\pm$ 0.24
Age range	18-35 years
Sex	Mixed
Race	100% black
Religion	100% Christian

Values = mean $\pm$ SEM

The phytochemical analysis of the fresh palm wine showed that it contained 4% alcohol, sugar

at a concentration of 22.32 ppm, saponins (105.00 ppm), tannins (2.05 ppm) and flavonoids (20600.00 ppm) (Table 2).

Table 2. Phytochemical analysis of fresh palm wine

Phytochemical constituent	Concentration
Sugar	22.32 ppm
Alcohol	4%
Saponins	10500.00 ppm
Tannins	2.05 ppm
Flavonoids	20600.00 ppm

Note – Phytochemicals present in palm wine and their quantities

Table 3 shows the effects of administration of artesunate and palm wine on serum electrolytes. After 7 days, there was a significant increase ($p<0.05$) in the serum Na^+ concentration of the participants administered artesunate and palm wine compared to their pre-treatment values. A similar trend was observed for the palm wine the only group. That of artesunate only group showed no significant difference. The serum K^+ concentration of both the palm wine and artesunate and palm wine only groups were significantly decreased ($p<0.05$) after 7 days of administration compared to their pre-treatment values. However, no significant difference was observed in the artesunate only group. No significant difference was observed in the post-treatment serum Cl^- and HCO_3^- concentration of the various experimental groups.

Table 4 shows the effects of administration of palm wine and artesunate on serum urea and creatinine levels. The serum creatinine concentration of palm wine and artesunate group was significantly increased ($p<0.05$) compared to their pre-treatment value. A similar result was obtained for the artesunate only group. No significant difference was observed in the palm wine the only group. The serum urea concentration of the palm wine and artesunate group was significantly increased ($p<0.05$) compared to its pre treatment value. However, no significant difference was observed in the values of the palm wine only and artesunate only groups compared to their pre-treatment values.

Table 3. Effects of palm wine and artesunate on some serum electrolytes

Groups	Na^+(mmol/L)	K^+(mmol/L)	Cl^-(mmol/L)	HCO_3^-(mmol/L)
Palm wine +artesunate				
Pre treatment	125.01 ± 2.99	4.14 ± 0.23	88.56 ± 3.35	26.89 ± 0.42
Post treatment	132.60 ± 2.05*	3.52 ± 0.26*	92.78 ± 2.21	26.10 ± 0.04
Palm wine				
Pre treatment	123.11 ± 0.31	4.81 ± 0.45	92.01 ± 3.62	26.20 ± 0.41
Post treatment	133.60 ± 2.25*	3.02 ± 0.39*	94.20 ± 2.51	26.20 ± 0.33
Artesunate				
Pre treatment	127.77 ± 4.69	5.01 ± 0.56	94.80 ± 5.19	26.61 ± 0.31
Post treatment	128.84 ± 1.91	3.38 ± 0.36	90.40 ± 2.34	27.01 ± 0.47

**Significantly different from pre treatment (P < .05). n= 10, values are presented as mean ± SEM*

Table 4. Effects of palm wine and artesunate on serum urea and creatinine concentration (mmol/L)

Groups	Urea	Creatinine
Palm wine + artesunate		
Pretreatment	4.34 ± 0.80	97.67 ± 14.16
Post-treatment	5.08 ± 0.37*	136.94 ± 13.86*
Palm wine		
Pretreatment	4.38 ± 0.03	111.57 ± 13.92
Post-treatment	4.70 ± 0.60	105.16 ± 8.42
Artesunate		
Pre treatment	4.88 ± 0.30	95.42 ± 14.39
Post treatment	4.61 ± 0.20	105.70 ± 9.74*

**Significantly different from pre treatment (P < .05). n=10, values are presented as mean ± SEM*

Table 5 shows the effect of administration of palm wine and artesunate on creatinine clearance. The post-treatment creatinine clearance for the palm wine and artesunate group was significantly decreased ($p<0.05$) compared to its pre-treatment value. The similar effect was observed in the artesunate only group. The value for the palm wine group was not significantly different.

Table 5. Effects of palm wine and artesunate on creatinine clearance (mL/minute)

Groups	Creatinine clearance
Palm wine + artesunate	
Pretreatment	102.78 ± 13.14
Post-treatment	68.95 ± 7.83*
Palm wine	
Pre treatment	81.60 ± 8.02
Post treatment	82.87 ± 7.86
Artesunate	
Pre treatment	98.64 ± 16.68
Post treatment	75.70 ± 6.80*

**Significantly different from pre treatment (P < .05). n=10, values are presented as mean ± SEM*

4. DISCUSSION

Phytochemical analysis of palm wine revealed the presence of alcohol, sugar, saponins, tannins and flavonoids. For serum electrolytes; the results showed that while the serum Na^+ concentration of artesunate only group showed no significant difference, those of both palm wine only and palm wine and artesunate groups were significantly higher compared to their pre-treatment values. This may be due to diuresis induced by alcohol in the palm wine [6,14]. Acute administration of alcohol has been reported to cause not only a marked urinary flow [15,16] but consistent falls in the excretion of sodium, chloride and potassium in humans [6]. Decreased Na^+ and/ or high plasma K^+ concentration would then stimulate the release of aldosterone which would favour K^+ excretion and Na^+ retention [17] as observed in this study.

Serum chloride was not significantly different in the 3 groups studied. Similarly, bicarbonate ions in the serum which are responsible for the maintenance of the pH of the extracellular fluid were not different in palm wine only, artesunate only and palm wine and artesunate groups. This is consistent with the report that artesunate administration in humans does not affect renal function [15]. However, studies in rats revealed that acute infusion of artesunate increases the urinary excretion of Na, Cl and K which was attributed in part to inhibition of Cl transport in the thick ascending limb of Henle [18].

Creatinine concentration in plasma was raised in the palm wine and artesunate group in this study. Artesunate treatment in rats has been associated with raised plasma creatinine [19]. Creatinine, a chemical product of protein metabolism is formed by the non-enzymatic hydration of creatine phosphate [20]. It is generated from muscle metabolism and serves as an important indicator of renal health [21]. The rate of its formation is fairly constant and it is chiefly cleared from the body through the kidneys. Raised plasma levels are therefore indicative of an impairment in renal function as evidenced by the decreased clearance (glomerular filtration rate) seen in this study.

Estimated glomerular filtration rate was significantly decreased in palm wine and artesunate group as well as in artesunate only group in this study. This is consistent with a study [18] which reported decreased glomerular rate in rats infused with artesunate. This decreased GFR may be due to a reduction in tubular reabsorption, thus leading to an increase in the pressure of the proximal tubule [22]. Increased tubular pressure reduces the net driving force for filtration and reduces glomerular filtration rate in the absence of a compensatory increase in glomerular hydrostatic pressure [23].

The reduction in GFR of the palm wine and artesunate group is greater than that seen in palm wine only and artesunate only groups, suggestive of an additive effect of palm wine and artesunate on renal function.

5. CONCLUSION

As observed in this study, combined intake of palm wine and artesunate may impose deleterious effects on the kidneys. This may, in the long run, culminate in renal failure. Combined or prolonged intake of palm wine and artesunate should be discouraged. Results of the present study may be of relevance to patients and healthy individuals alike to desist from consumption of drug combinations that have renal adverse effects.

LIMITATION OF STUDY

The number of participants in each group is small.

CONSENT

Informed written consent was obtained from each participant.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards aid down in 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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